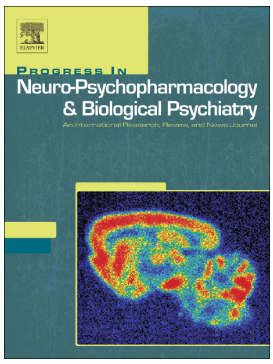
Accepted Manuscript



Functional MRI findings, pharmacological treatment in major depression and clinical response

Danilo Arnone

PII: S0278-5846(18)30128-3
DOI: doi:10.1016/j.pnpbp.2018.08.004
Reference: PNP 9464

To appear in: *Progress in Neuropsychopharmacology & Biological Psychiatry*

Received date: 27 February 2018
Revised date: 20 July 2018
Accepted date: 8 August 2018

Please cite this article as: Danilo Arnone , Functional MRI findings, pharmacological treatment in major depression and clinical response. Pnp (2018), doi:10.1016/j.pnpbp.2018.08.004

Functional MRI findings, pharmacological treatment in major depression and clinical response

Danilo Arnone* danilo.arnone@kcl.ac.uk

Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, Centre for affective Disorders, King's College London, London UK and South London and Maudsley NHS Foundation Trust

*Corresponding author.

Abstract

Major depressive disorders are common conditions with relatively limited response to treatment. In order to improve response to treatment, a better understanding of functional neuroanatomy is necessary to improve treatment targets at brain level. This work summarises the literature of longitudinal functional magnetic resonance imaging studies in major depression to identify brain regions where aberrant neural activity normalises after clinical response following treatment with pharmacological compounds with known antidepressant properties. Hyperactivity in regions such as the amygdala and the ventral components of the anterior cingulate cortex were some of the most replicated findings of functional MRI studies in major depression and normalisation of aberrant activity one of the best predictive biomarkers of treatment response.

Keywords: MRI, Major depression, functional MRI, antidepressants

1. Introduction

Major depressive disorders are common conditions affecting approximately 10% of the population (McKenna et al, 2005) likely to became second only to ischemic heart disease in terms of disability by 2020 (Lopez et al., 2006)(Murray and Lopez, 1997). Treatment modalities which include a range of psychological and pharmacological interventions, achieve a clinical response in the range of 50-60% of cases and remission in approximately 20-30% (Warden et al., 2007). Novel research is necessary to further characterise the biological underpinning of depressive disorders to specifically identify brain systems to model mood dysregulation and offer new therapeutic targets. Brain structure and function are the end product of emotional behaviours originating from environmental effects and epigenetic adaptations (Vanderwolf, 1998). Research in affective disorders has taken advantage of a range of magnetic resonance imaging (MRI) techniques to investigate mood disorders and response to treatment (Harmer, 2008)(Wise et al., 2014). Functional MRI techniques allow to study brain activity in response to neuropsychological tasks but also at rest. Affective cognitive neuroscience allows characterisation in vivo of brain regions involved in cognitive and emotional functions. In this context, experiments are designed to evaluate cognitive processes and assess systems reliant on the processing of emotions by eliciting emotion recognition or suppression (Elliott et al., 2011). This work summarises the literature of functional MRI studies in major depression which used a longitudinal design to identify clinical response following treatment with pharmacological compounds with known antidepressant properties.

2. Methods

The aim of the work was to select studies which identified brain regions with aberrant neural baseline activity that either normalised following pharmacological treatment and clinical response or persisted as an indicator of treatment refractoriness. Functional neuroimaging studies were identified by searching Medline, Embase and Scopus from the year 2000 to February 2018. Key words used in combination included ‘functional magnetic resonance’ or ‘fMRI’, ‘major depression’, ‘depressive disorders’, ‘antidepressants’, ‘emotion’, ‘affective

neuroscience'. Identified articles were cross referenced. Functional MRI studies were included if 1) written in English, 2) investigated the effect of pharmacological compounds currently licenced to treat major depression administered to currently depressed individuals diagnosed according to established diagnostic systems, 3) contained matched cases and controls, 4) involved at least two MRI sessions before and after pharmacological treatment, 5) pharmacological treatment was commenced after baseline MRI scan, 6) Patients were not treatment resistant. Group x time interactions were reported as far as possible to minimise mere habituation effects.

3. Results

The searches identified over 600 reports, 93 studies were scrutinised of which 31 met inclusion criteria. Of these 18 used emotion processing tasks, 7 used non-emotional tasks and 6 used resting state functional MRI techniques. The majority of the studies were excluded because lacked longitudinal MRI data. Reports were also excluded because individuals were not necessarily treatment free at the time of scanning (Keedwell et al., 2009)(Keedwell et al., 2010), cases and controls were not matched (Andreescu et al., 2013), primarily included patients with dysthymia or remitted depression rather than current major depression (Posner et al., 2013), (Smith et al., 2017), did not include a group of healthy controls in the longitudinal analyses (Lisiecka et al., 2011), (Jiang et al., 2012), (Miller et al., 2013), (Chen et al., 2007), (Robertson et al., 2007), (Yang et al., 2014), (Miskowiak et al., 2016a), (Miskowiak et al., 2016b) (Ramasubbu et al., 2016), (Carhart-Harris et al., 2017), (Karim et al., 2017)(Frodl et al., 2011)(Samson et al., 2011), investigated adolescents (Tao et al., 2012), were superseded by more recent reports or data were included in other reports (Fu et al., 2008)(Light et al., 2011)(Godlewska et al., 2012)(Wang et al., 2014a) (Wang et al., 2014b)(Fang et al., 2015), (Ruhé et al., 2014)(An et al., 2017)(Wang et al., 2017), used polypharmacy (Rizvi et al., 2013), tested experimental pharmacological interventions (Furey et al., 2013)(Furey et al., 2015), investigated treatment resistant patients (Murrough et al., 2015)(Abdallah et al., 2017), implemented a multivariate pattern of analysis (Qin et al., 2015), did not exclude pathology in controls (Aizenstein et al., 2009).

3.1 Functional MRI antidepressant treatment studies with emotion processing tasks

This group of studies investigated the effect of pharmacological treatment in major depression vs. healthy controls by using a range of neuropsychological tasks which triggered networks

implicated in the processing of emotion and emotion regulation. The large majority of this research utilised faces or pictures expressing graded (Young et al., 1997), validated (e.g. Ekman and Friesen, 1971) positive and negative emotions presented in the MRI scanner implicitly or explicitly, openly recognised or covertly presented to avoid suppression mechanisms (Elliott et al., 2011). Analyses commonly contrasted individual emotions vs. neutral stimuli, vs. opposite emotions or vs. baseline brain activity measured at multiple time points. These studies are described below and detailed in Table 1.

Sheline and others used masked face emotions including happy, fearful and neutral to test the selective serotonin reuptake inhibitor (SSRI) Sertraline. Neural activity was increased in depression in the left amygdala at baseline which decreased after 8-week of treatment in response to fearful faces in bilateral amygdala (Sheline et al., 2001).

In Davidson's study depressed patients after viewing emotional pictures, showed reduced activation in left insula and left anterior cingulate cortex with negative vs. neutral contrast which increased after 2 weeks of treatment with the serotonin and noradrenalin reuptake inhibitor (SNRI) Venlafaxine. Changes in the anterior cingulate cortex were predictive of treatment response at week 8 (Davidson et al., 2003).

Fu and others investigated the effects of Fluoxetine for 8 weeks on implicit processing of emotional faces in two separate papers with sad and happy vs. neutral contrast. With sad faces increased neural activity in depression was reduced after treatment in the amygdala, ventral striatum, insula, caudate nucleus, thalamus, dorsal and posterior cingulate cortex, precentral gyrus extending to the lateral premotor cortex, postcentral gyrus, and inferior parietal lobule (Fu et al., 2004). With happy faces a reduced dynamic range which increased significantly after treatment was reported in the lingual gyri and cuneus, extending to the precuneus and posterior cingulate gyrus bilaterally (Fu et al., 2007).

Schaefer and colleagues measured neural responses to viewing emotional pictures which showed social interaction, facial expressions and erotic pictures. Depressed subjects were characterised by a reduction in neural activity in response to positive social stimuli in a range of regions including prefrontal, temporal, parietal cortices, insula, basal ganglia and the hippocampus which tended to reach levels comparable to healthy controls following 22 weeks treatment with Venlafaxine. In case of pictures showing social interactions, the regions included the inferior, medial, and superior frontal gyri, superior temporal gyrus, supramarginal gyrus, caudate, hippocampus with additional significant clusters in the right ventrolateral thalamic nucleus, bilateral putamen, right middle and inferior temporal gyri, and posterior cingulate (Schaefer et al., 2006).

Anand and colleagues administered Sertraline for 6 weeks and tested participants with emotionally evocative pictures. Following treatment, a decrease in neural activity was noted in overactive predefined regions of interest including pregenual anterior cingulate cortex, medial thalamus, pallido-striatum, amygdala with the negative vs. neutral contrast (Anand et al., 2007).

Fales and others used an emotion interference task to test the effect of Escitalopram, Sertraline or Paroxetine for 8 weeks. When ignoring fearful faces, depressed patients showed reduced neural activity in the right dorsolateral prefrontal cortex whereas neural activity was increased in the left amygdala at baseline. Neural activity normalised after treatment in these regions (Fales et al., 2009).

Victor and colleagues, investigated the effect of Sertraline for 8 weeks with a backword masking face emotion processing task. Masked sad vs. neutral faces at baseline elicited increased neural activity in the amygdala in depression which attenuated with treatment. Responses to masked happy vs. neutral faces increased in the same region in depression and inversely correlated with depression severity score (Victor et al., 2010).

With a similar design, Arnone and others treated depressed patients with Citalopram for 8 weeks and used an implicit face emotion processing task. Currently depressed patients showed increased neural activity in the amygdala with the sad vs. neutral contrast at baseline which normalised following treatment (Danilo Arnone et al., 2012).

Rosenblau and colleagues tested brain responses to 8 weeks treatment with Escitalopram by using emotional pictures presented with a cue indicating their emotional valence (expected) or with random letters (unexpected). The main results indicated increased neural activity in the amygdala when anticipating negative pictures and greater prefrontal activation (dorsolateral prefrontal cortex and orbitofrontal cortex) in depression when negative pictures were presented with no anticipatory cues. Both effects decreased after antidepressant treatment (Rosenblau et al., 2012).

Another study by Ruhé and others investigated patients treated with Paroxetine for 12 weeks with scans at week-6 and 12 by using an implicit face emotion processing task. At baseline patients showed enhanced amygdala activation in response to negative faces which decreased at endpoint in responders (Ruhé et al., 2012).

Wang and others administered Fluoxetine for 8 weeks and participants were required to explicitly respond to emotional pictures. With positive pictures, neural activity was reduced in the right insula, left caudate head and left anterior cingulate cortex after antidepressant treatment. In response to negative pictures, following treatment, patients exhibited greater

activation in the right middle frontal gyrus, right inferior temporal gyrus, right precuneus and inferior parietal lobule (Wang et al., 2012).

Heller and others investigated individuals exposed to positive and negative pictures randomly treated with Venlafaxine (N=12) or Fluoxetine (N=9) for 2 months. Following treatment, the largest increases in sustained activity was measured in the nucleus accumbens in response to positive viewing. Connectivity between the nucleus accumbens and left middle frontal gyrus, ventromedial prefrontal cortex and right anterior insula also increased with the same emotional induction (Heller et al., 2013).

Victor and colleagues used a backward masking task to elicit neural responses to implicit emotional faces in patients treated with Sertraline for 8 weeks. Greater responses in depression to masked sad vs. happy and masked sad vs. neutral faces in the right pregenual anterior cingulate cortex normalised post-treatment. Greater neural activity in this region in response to masked sad vs. happy faces at baseline was predictive of a greater reduction in depression severity during the course of treatment (Victor et al., 2013).

Fu and colleagues investigated response to the SNRI Duloxetine at weeks 1, 8 and 12 with an emotional Stroop and face emotion processing tasks. Only the emotional Stroop induced a significant increase in neural activity after treatment in the left posterior temporo-parietal junction involving the parahippocampal cortex as well as precuneus and posterior cingulate cortex during the processing of negative vs. neutral words (Fu et al., 2015).

Williams and others measured neural responses to positive and negative emotional faces presented both above and below conscious discrimination. Depressed individuals were randomised to receive Escitalopram, Sertraline, or Venlafaxine extended release for 8 weeks. Responders showed a decrease in neural responses in bilateral amygdala to happiness and to fear and anger in the left amygdala (Williams et al., 2015).

Delaveau and others investigated the effects of Agomelatine and participants were presented with pictures with equal positive, negative and neutral valence requiring self-relevant or general responses. By contrasting the self vs. general responses, patients on Agomelatine showed a significant tendency to decrease neural activity in the ventrolateral prefrontal cortex from baseline to week 1. After 7 weeks, increased activation was noted in the ventral anterior cingulate cortex and decreased in the dorsolateral prefrontal cortex (Delaveau et al., 2016).

Godlewska and colleagues employed an implicit face emotional processing task combined with treatment with escitalopram for 6 weeks. After 7 days of treatment a decrease in neural response was noted in response to fearful vs. happy faces in the left amygdala, insula, anterior

and posterior cingulate cortices, bilateral supra-marginal gyri and bilateral thalamus (Godlewska et al., 2016).

In summary the majority of the studies identified investigated pharmacological effects of SSRIs and/or SNRIs with the exception of Agomelatine and it is not possible to reliably identify a specific pattern at brain level for a pharmacological class of compounds. The majority of patients also responded of remitted following treatment. It follows that the biological characterisation of non-responders is challenging. The interval between MRI scans ranged from 2 to 22 weeks with a mode of 8. There were substantial methodological differences across the studies which limit comparability and generalisability. Tasks, particularly with negative emotions, especially if implicitly administered, often showed enhanced neural activity in the amygdala in major depression (~50% of studies) and the anterior cingulate cortex (~30% of studies). Increased neural activity was also shown in extended circuitry including regions such as the ventral striatum, the thalamus, the nucleus accumbens, dorsal parts of the cingulate cortex and the insula. There was a tendency to the opposite effect with positive stimuli in the amygdala and in other regions such as the insula and basal ganglia. Neural activity in the hippocampus and thalamus was shown to be reduced in some of these studies with positive emotions also. Tasks which engaged cognitive processes, especially those evoking an emotional response, tended to elicit increased neural activity in a number of cortical regions including ventromedial and orbitofrontal regions and decreased activity in dorsolateral and ventrolateral cortices which varied in relation to the intensity of the signal and sometimes in the direction depending on the task used, the emotion valence and the presence of a self-referential element. Tasks which triggered anticipatory cues appeared associated with greater prefrontal activation. The presence of an interference task and emotional distracters resulted in decreased neural activation in cortical and subcortical areas including the amygdala, except the emotional Stroop task shown to be associated with greater activation in posterior cingulate cortex and precuneus. Based on the information available, major depression is particularly associated with baseline abnormalities in neural activity in the amygdala and anterior cingulate cortex which tend to normalise after treatment and clinical response. Greater abnormalities in these regions at baseline and the degree on normalisation appear the best predictors of clinical response with persistence of abnormalities in non-responders.

3.2 Functional MRI antidepressant treatment studies with non-emotional tasks

The studies described below examined neural responses in major depression before and after antidepressant treatment in response to non-emotional stimuli including cognitive and reward processes. Details of the methods adopted in the studies are described below and in Table 2.

Walsh and colleagues investigated the effects of 8-week treatment with Fluoxetine on working memory performance by using an N-back verbal working memory task. A significant increase in the quadratic load response activity was reported in the left caudate and right thalamus following treatment (Walsh et al., 2007).

In another study a task to judge self vs. general condition was used to test the pharmacological effects of SSRIs, SNRIs and tricyclics administered for 9 weeks. The study was based on the notion that a qualitative cognitive bias towards the self can affect medial prefrontal neural responses in major depression. The authors reported attenuation in neural activity in the left dorsolateral prefrontal cortex with the self vs. general condition in depressed patients and sustained greater activation of the dorsal medial frontal gyrus with the same condition after treatment (Lemogne et al., 2010).

López-Solà and others investigated pain symptoms in major depression in response to 8-week treatment with Duloxetine by using a pain induction task. Patients showed greater baseline activation in bilateral insula, medial prefrontal cortex, middle temporal gyrus, frontal and temporal opercula, left hippocampus, ventral basal ganglia, hypothalamic region, and abnormal persistence of activity during stimulation in a large area involving the subgenual and pregenual anterior cingulate cortex and extended medial prefrontal regions. After treatment there was a reduction in neural activity involving a similar network and the brainstem including the anterior and posterior parts of the pons. Reductions in symptoms of depression after 1 week of treatment were significantly correlated with activation reductions in the pregenual anterior cingulate cortex. Reductions in somatic symptoms were significantly correlated with activation reductions in the right dorsolateral prefrontal cortex. Improvement in depressive symptoms after 8 weeks of treatment correlated with activation reductions in the right dorsolateral prefrontal cortex and left insulo-opercular region. Remitters had greater activation reductions in the pons after 8 weeks of treatment (López-Solà et al., 2010).

Wagner and colleagues used the Stroop Color-Word test to investigate neural activity in the rostral anterior cingulate cortex in relation to emotional interference following a course of the noradrenaline reuptake inhibitor (NRI) Reboxetine or Citalopram for a period of 6 weeks. A

predominant reduction in the activity of the amygdala–hippocampus complex was attributed to Citalopram (Wagner et al., 2010).

Stoy and others investigated neural responses to Escitalopram for 6 weeks with a monetary incentive delay task which targeted the ventral striatum involved in response to reward as a proxy of hedonic tone. Patients showed decreased ventral striatal activation during anticipation of gain and loss which ameliorated with treatment and was associated with self-reported measures of severity of depression and anhedonic symptoms (Stoy et al., 2012).

Gyurak and colleagues assessed inhibitory control by using a Go/NoGo task, selective attention with the oddball task and selective working memory by using the continuous performance task. Depressed individuals were randomised to receive Escitalopram, Sertraline, or Venlafaxine extended release and tested at baseline and after 8 weeks. Non-remitters showed hypoactivation in the dorsolateral prefrontal cortex with the inhibitory NoGo task (Gyurak et al., 2016).

Sankar and colleagues treated patients with Duloxetine for 12 weeks and tested neural responses to verbal working memory by using the Sternberg task. Authors reported reduced activation in healthy participants at end point and no changes in affected individuals in the left middle frontal gyrus, the right middle cingulum, left inferior temporal gyrus, right superior temporal pole, caudate, right thalamus, and cerebellum (Sankar et al., 2017).

In summary, the majority of studies used SSRIs, SNRI and NRI for 6-12 weeks in combination with a variety of tasks. It is not possible to establish a clearly distinctive pattern in relation to pharmacotherapy although citalopram was associated with reduction in neural activity in the amygdala–hippocampus complex in one study suggesting a preferential normalising effect compared to Reboxetine. The majority of patients largely responded and remitted following treatment so that it is difficult to ascertain a clear pattern for non-responders. Attenuation of neural activity in the dorsolateral prefrontal cortex was reported in ~43% of the studies with a self-referential task, a pain induction task (which also evoked responses in a wide network including the insula) and an inhibition task (reported in non-responders). This abnormality normalised following pharmacotherapy and clinical response. Other noticeable brain regions included the rostral anterior cingulate cortex where increased neural activity was measured with an emotion interference task and the ventral striatum where decreased activation was shown with a reward task. Overall neural differences in major depression tended to attenuate following treatment and clinical response and persistence of

abnormalities in the dorsolateral prefrontal cortex was associated with non-response. Change in neural activity in these regions did not seem to show a specific pattern predictive of response.

3.3 Resting state analysis

These are studies that used resting state functional connectivity methods. In the absence of any specific task executed in the MRI scanner, these experiments were designed to evaluate changes in the blood oxygen level dependent signal in brain networks or regions of interest at rest. Methods available in the literature include the evaluation of synchronisation of regional activation, measures of regional homogeneity, temporal correlations between a defined 'a priory' region of interest with other voxels in the brain, and data driven analyses. Details of the studies are described below and in Table 3.

Anand and others treated patients with Sertraline for 6 weeks. Decreased connectivity at baseline between the anterior cingulate cortex and left and right medial thalamus and pallidostriatum increased at the end of the study (Anand et al., 2005).

After treatment with Duloxetine for 6 weeks Lai and colleagues showed that in major depression regional homogeneity increased in the right superior frontal cortex but also in the right medial frontal cortex and decreased in the right superior temporal cortex. Changes mildly correlated with improvement of symptoms (Lai and Wu, 2012).

Li et al., investigated resting state activation following 12-week treatment with Paroxetine, Citalopram, Venlafaxine or Duloxetine with only a subgroup of patients scanned twice (N=16). At baseline increased connectivity was measured in a posterior network comprising the bilateral precuneus and in an anterior network which included the medial prefrontal cortex. Following treatment only connectivity in the posterior network normalised (Li et al., 2013).

The effect of Duloxetine was investigated in a multimodal study (Fu et al., 2015 also described in Section 3.1). Independent functional analyses indicated that over time connectivity decreased in the default mode network between right dorsolateral cortex, right superior frontal premotor cortex and left inferior frontal gyrus. Decreased connectivity was also noted in the auditory processing cortex and the primary visual and extrastriate regions. Connectivity increased between medial prefrontal regions, including pregenual and subgenual cingulate and the frontal pole, parahippocampal gyrus, angular gyrus, and middle occipital gyrus (Fu et al., 2015).

Wang and colleagues investigated Escitalopram over 8 weeks. Functional connectivity strength increased in the bilateral dorsomedial prefrontal cortex at baseline, correlated with severity depression scores and reduced following treatment and clinical response. Functional connectivity strength in the bilateral hippocampus followed an inverse pattern whereby baseline lower functional connectivity strength subsequently increased (Wang et al., 2015).
Resting state connectivity following treatment with Escitalopram at baseline, after 5 hours, 4 weeks and 8 weeks was evaluated by Cheng and associates. Following acute (5H) and sub-chronic (4W and 8W) treatment administration the signal decreased in the bilateral post-central gyrus and left superior temporal gyrus and increased in a vast area of the prefrontal cortex incorporating dorsomedial and dorsolateral regions (Cheng et al., 2017).

In summary, these studies investigated a range of pharmacological interventions mostly involving SSRIs and SNRIs for a period of 24 hours-12 weeks. It is not possible to establish a distinctive pattern in relation to pharmacotherapy. There was a noticeable trend suggestive of increased functional connectivity between frontal and limbic brain regions and decreased functional connectivity following treatment between medial prefrontal regions and dorsomedial and dorsolateral cortices overlapping with areas within the default mode network. These findings suggest that treatment and clinical response might contribute to improve top-down control over emotional responses and ruminative thought patterns (Perkins et al., 2015).

4. Conclusion and future directions

This work reviewed the literature pertinent to functional MRI studies investigating changes in brain regions in major depression, the relationship to pharmacological treatment and clinical response. The large majority of the studies with a longitudinal approach used neuropsychological tasks to test emotional circuitry, a few investigated a range of cognitive functions and a small group of studies examined neural response at rest. The main obstacle in attempting to generalise findings across the identified studies is that design differed significantly, a variety of approaches were used including different tasks, the length of the studies and pharmacological compounds varied, and several emotions and contrasts were used. Further limitations include methodological differences across the studies e.g. resting state functional connectivity instructions, scan acquisition parameters (e.g. TR, amount of volumes, etc.) which are known to affect both data quality and analyses results. Furthermore, as studies had a longitudinal design, it is possible that task habituation occurred in emotional

processing studies in studies where group x time interactions were not clearly described. Another observation is the high rate of response and remission across the studies which limits our understanding of the neurobiology of treatment refractoriness and perhaps suggests the possibility that milder forms of major depression were selected.

With all these limitations, functional MRI studies with emotion processing tasks tend to show that especially in response to negative visual stimuli, neural hyperactivity is often detected in prefrontal areas including ventromedial, anterior cingulate and orbitofrontal cortices whilst subcortical brain regions such as the amygdala and ventral striatum tend to be seemingly overactive with a tendency in both cases to normalisation following pharmacological treatment. Neural activity in the hippocampus and parahippocampal gyrus seem to be reduced whereas neural activity in pregenual and the most ventral components of the anterior cingulate cortex has been shown to be increased. The most replicated predictors of treatment response included the amygdala and the ventral part of the anterior cingulate cortex. These are the regions where greater neural activity at baseline or degree on change during treatment are more likely to predict treatment response following treatment. Responses elicited to positive stimuli appeared less preponderant in the literature in major depression supporting the notion of selective attending of negative (e.g. sadness, fear) over positive stimuli (e.g. happiness). When response to positive stimuli was elicited, neural activity in the subcortical regions and limbic areas appeared reduced prior to treatment, with a tendency to normalise following pharmacological interventions. Patterns overall were less distinctive when more complex tasks or explicit tasks with longer time of exposure to stimuli were used, favouring the involvement of cognitive processes. This is because when emotional information is presented subliminally, it is processed independently from attention and also rapidly, automatically and unconsciously (Pessoa and Adolphs, 2010). Inevitably, tasks that allow longer exposures to attend emotions, are likely to trigger more complex feedback systems involving cortical regions such as the orbitofrontal cortex and neural signals become less consistent across the studies (Ohman, 2005).

Results from functional MRI studies which used tasks to test cognitive functions suggest that prefrontal areas tend to hypofunction under performance in major depression and reductions in neural activity in the dorsolateral prefrontal cortex tends to normalise following response. Greater neural activity in the ventral striatum at baseline which normalised following treatment correlated with depressive symptoms. In these groups of studies, it is not possible to identify specific patterns in relation to pharmacological compounds or predictors of treatment response. Resting state studies indicated enhanced functional connectivity following treatment

between frontal and limbic brain regions, possibly reflecting an increase in inhibitory top-down control over emotional responses exercised by prefrontal cortices over key limbic regions involved in regulation of emotions. At the same time a reduction in connectivity between medial prefrontal cortex and dorsal prefrontal cortices following treatment is suggestive of increased baseline functional activity in major depression within the default mode network, in agreement with recent research findings (Wise et al., 2017a). Response to treatment might therefore ameliorate these abnormalities which might be reflective of ruminative thought patterns (Perkins et al., 2015).

Finding from these studies are consistent with described biological models of depression which advocate the importance of the integration of information across different anatomical brain sectors to ensure homeostatic emotion regulation. Anatomical compartments include a cognitive element essential in regulating responses to emotional stimuli overtly presented and a viscero-motor sector mediating covert responses (Mayberg, 1997)(Mayberg, 2009)(Arnone et al., 2016)(Wise et al., 2014). Subcortical areas such as the thalamus and the ventral striatum appear functionally active in the processing of emotional information (Mayberg, 2009), coexisting with regulatory activity in prefrontal regions exercising cognitive control and conscious appraisal on any given emotional state (Adolphs, 2002) (Mayberg, 2009)(Phillips et al., 2003). In a depressed state an overactive 'bottom-up' brain circuitry characterised by over-functional key regions such as the amygdala and the anterior cingulate cortex coexist with underactive 'top-down' cortical control which includes regions in the medial and orbital part of the prefrontal brain (Figure 1) (Adolphs, 2002) (Mayberg, 2009)(Phillips et al., 2003)(Roiser et al., 2012). Overactivity in key regions within the default mode might contribute to explain a ruminative thought pattern (Perkins et al., 2015). The involvement of these regions has been extensively reported in the literature also in structural MRI studies (D Arnone et al., 2012) (Toby Wise et al., 2018) across mood disorders (Wise et al., 2017b). Pharmacotherapy and clinical response appear to contribute to achieve an equilibrium compatible with normalisation of baseline aberrant neural activities.

In summary studies described a range of abnormalities in cortical and subcortical brain regions in major depression. This is in agreement with models described in this condition and could contribute to explain cognitive bias, abnormalities in executive and working memory functions described in depressive disorders and response to treatment (Mayberg, 1997)(Phillips et al., 2003)(Roiser et al., 2012). Hyperactivity in the amygdala and the ventral

components of the anterior cingulate cortex are the most replicated findings of functional MRI studies in major depression and some of the best predictive biomarkers of treatment response. Future work requires standardisation of procedures and methodologies. The development of a central depository of standardised neuroimaging data to carry out analyses of large datasets could help dilute the effects of confounders by increasing validity and generalisability of the results.

Acknowledgements

Dr Arnone has received support from the Academy of Medical Sciences, UK (grant no. AMS-SGCL8).

Ethical statement

Dr Arnone has received travel grants from Jansen-Cilag and Servier and sponsorship from Lundbeck.

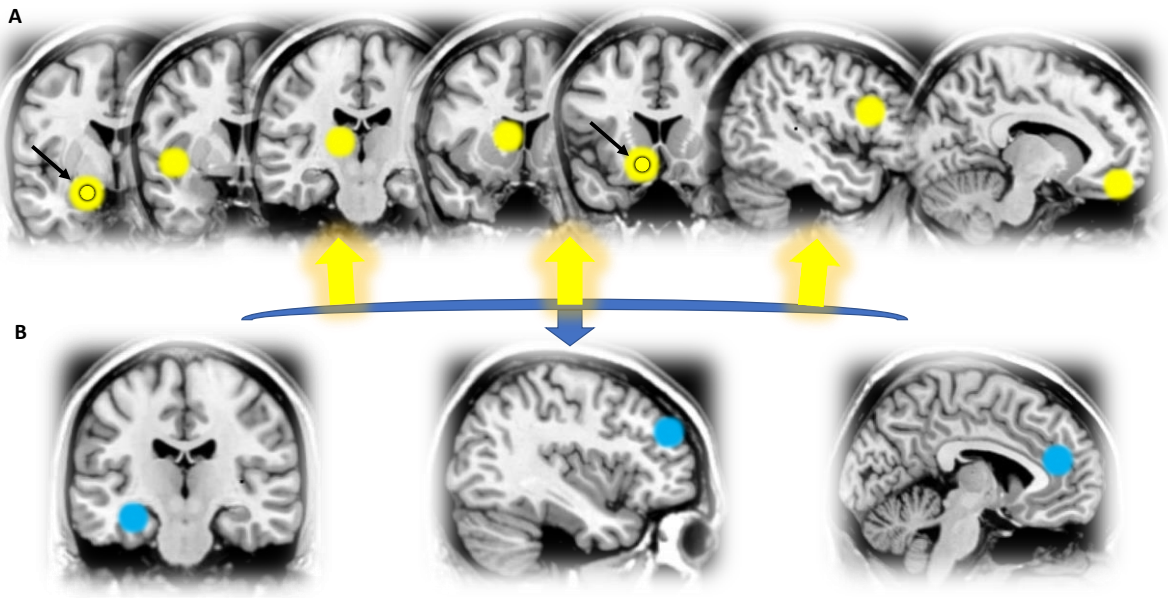


Figure 1: Schematic interpretation of the results of the neuroimaging studies in major depression based on theoretical models which suggest an interplay between brain regions with reduced activity (inhibitory=blue) and increased activity (yellow) resulting in cognitive and emotional changes (Phillips et al., 2003) (Mayberg, 1997). **A: brain regions with increased neural activity.** From left to right: amygdala, insula, medial thalamus, ventral anterior cingulate cortex, dorsolateral prefrontal cortex, orbitofrontal cortex. **B: brain regions with decreased neural activity.** From left to right: Hippocampus, dorsolateral prefrontal cortex, dorsal part of the ventromedial prefrontal cortex. Circles and black arrows indicate brain regions most likely to be predictive of treatment response (amygdala and ventral anterior cingulate cortex).

References

Abdallah, C.G., Averill, L.A., Collins, K.A., Geha, P., Schwartz, J., Averill, C., DeWilde, K.E., Wong, E., Anticevic, A., Tang, C.Y., Iosifescu, D.V., Charney, D.S., Murrough, J.W., 2017. Ketamine Treatment and Global Brain Connectivity in Major Depression. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 42, 1210–1219. https://doi.org/10.1038/npp.2016.186

Adolphs, R., 2002. Neural systems for recognizing emotion. Curr. Opin. Neurobiol. 12, 169–177.

Aizenstein, H.J., Butters, M.A., Wu, M., Mazurkewicz, L.M., Stenger, V.A., Gianaros, P.J., Becker, J.T., Reynolds, C.F., Carter, C.S., 2009. Altered functioning of the executive control circuit in late-life depression: episodic and persistent phenomena. Am. J. Geriatr. Psychiatry Off. J. Am. Assoc. Geriatr. Psychiatry 17, 30–42. https://doi.org/10.1097/JGP.0b013e31817b60af

An, J., Wang, L., Li, K., Zeng, Y., Su, Y., Jin, Z., Yu, X., Si, T., 2017. Differential effects of antidepressant treatment on long-range and short-range functional connectivity strength in patients with major depressive disorder. Sci. Rep. 7, 10214. https://doi.org/10.1038/s41598-017-10575-9

Anand, A., Li, Y., Wang, Y., Gardner, K., Lowe, M.J., 2007. Reciprocal effects of antidepressant treatment on activity and connectivity of the mood regulating circuit: an FMRI study. J. Neuropsychiatry Clin. Neurosci. 19, 274–282. https://doi.org/10.1176/jnp.2007.19.3.274

Anand, A., Li, Y., Wang, Y., Wu, J., Gao, S., Bukhari, L., Mathews, V.P., Kalnin, A., Lowe, M.J., 2005. Antidepressant effect on connectivity of the mood-regulating circuit: an FMRI study. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 30, 1334–1344. https://doi.org/10.1038/sj.npp.1300725

Andreescu, C., Tudorascu, D.L., Butters, M.A., Tamburo, E., Patel, M., Price, J., Karp, J.F., Reynolds, C.F., Aizenstein, H., 2013. Resting state functional connectivity and

treatment response in late-life depression. Psychiatry Res. 214, 313–321. https://doi.org/10.1016/j.pscychresns.2013.08.007

Arnone, D., Job, D., Selvaraj, S., Abe, O., Amico, F., Cheng, Y., Colloby, S.J., O'Brien, J.T., Frodl, T., Gotlib, I.H., Ham, B.-J., Kim, M.J., Koolschijn, P.C.M.P., Périco, C.A.-M., Salvadore, G., Thomas, A.J., Van Tol, M.-J., van der Wee, N.J.A., Veltman, D.J., Wagner, G., McIntosh, A.M., 2016. Computational meta-analysis of statistical parametric maps in major depression. Hum. Brain Mapp. 37, 1393–1404. https://doi.org/10.1002/hbm.23108

Arnone, D, McIntosh, A.M., Ebmeier, K.P., Munafò, M.R., Anderson, I.M., 2012. Magnetic resonance imaging studies in unipolar depression: systematic review and meta-regression analyses. Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol. 22, 1–16. https://doi.org/10.1016/j.euroneuro.2011.05.003

Arnone, Danilo, McKie, S., Elliott, R., Thomas, E.J., Downey, D., Juhasz, G., Williams, S.R., Deakin, J.F.W., Anderson, I.M., 2012. Increased amygdala responses to sad but not fearful faces in major depression: relation to mood state and pharmacological treatment. Am. J. Psychiatry 169, 841–850. https://doi.org/10.1176/appi.ajp.2012.11121774

Carhart-Harris, R.L., Roseman, L., Bolstridge, M., Demetriou, L., Pannekoek, J.N., Wall, M.B., Tanner, M., Kaelen, M., McGonigle, J., Murphy, K., Leech, R., Curran, H.V., Nutt, D.J., 2017. Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. Sci. Rep. 7, 13187. https://doi.org/10.1038/s41598-017-13282-7

Chen, C.-H., Ridler, K., Suckling, J., Williams, S., Fu, C.H.Y., Merlo-Pich, E., Bullmore, E., 2007. Brain imaging correlates of depressive symptom severity and predictors of symptom improvement after antidepressant treatment. Biol. Psychiatry 62, 407–414. https://doi.org/10.1016/j.biopsych.2006.09.018

Cheng, Y., Xu, J., Arnone, D., Nie, B., Yu, H., Jiang, H., Bai, Y., Luo, C., Campbell, R. a. A., Shan, B., Xu, L., Xu, X., 2017. Resting-state brain alteration after a single dose of SSRI administration predicts 8-week remission of patients with major depressive disorder. Psychol. Med. 47, 438–450. https://doi.org/10.1017/S0033291716002440

Davidson, R.J., Irwin, W., Anderle, M.J., Kalin, N.H., 2003. The neural substrates of affective processing in depressed patients treated with venlafaxine. Am. J. Psychiatry 160, 64–75. https://doi.org/10.1176/appi.ajp.160.1.64

Delaveau, P., Jabourian, M., Lemogne, C., Allaïli, N., Choucha, W., Girault, N., Lehericy, S., Laredo, J., Fossati, P., 2016. Antidepressant short-term and long-term brain effects during self-referential processing in major depression. Psychiatry Res. 247, 17–24. https://doi.org/10.1016/j.pscychresns.2015.11.007

Elliott, R., Zahn, R., Deakin, J.F.W., Anderson, I.M., 2011. Affective cognition and its disruption in mood disorders. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 36, 153–182. https://doi.org/10.1038/npp.2010.77

Fales, C.L., Barch, D.M., Rundle, M.M., Mintun, M.A., Mathews, J., Snyder, A.Z., Sheline, Y.I., 2009. Antidepressant treatment normalizes hypoactivity in dorsolateral prefrontal cortex during emotional interference processing in major depression. J. Affect. Disord. 112, 206–211. https://doi.org/10.1016/j.jad.2008.04.027

Fang, J., Mao, N., Jiang, X., Li, X., Wang, B., Wang, Q., 2015. Functional and Anatomical Brain Abnormalities and Effects of Antidepressant in Major Depressive Disorder: Combined Application of Voxel-Based Morphometry and Amplitude of Frequency

Fluctuation in Resting State. J. Comput. Assist. Tomogr. 39, 766–773. https://doi.org/10.1097/RCT.0000000000000264

Frodl, T., Scheuerecker, J., Schoepf, V., Linn, J., Koutsouleris, N., Bokde, A.L.W., Hampel, H., Möller, H.-J., Brückmann, H., Wiesmann, M., Meisenzahl, E., 2011. Different effects of mirtazapine and venlafaxine on brain activation: an open randomized controlled fMRI study. J. Clin. Psychiatry 72, 448–457. https://doi.org/10.4088/JCP.09m05393blu

Fu, C.H.Y., Costafreda, S.G., Sankar, A., Adams, T.M., Rasenick, M.M., Liu, P., Donati, R., Maglanoc, L.A., Horton, P., Marangell, L.B., 2015. Multimodal functional and structural neuroimaging investigation of major depressive disorder following treatment with duloxetine. BMC Psychiatry 15, 82. https://doi.org/10.1186/s12888-015-0457-2

Fu, C.H.Y., Mourao-Miranda, J., Costafreda, S.G., Khanna, A., Marquand, A.F., Williams, S.C.R., Brammer, M.J., 2008. Pattern classification of sad facial processing: toward the development of neurobiological markers in depression. Biol. Psychiatry 63, 656–662. https://doi.org/10.1016/j.biopsych.2007.08.020

Fu, C.H.Y., Williams, S.C.R., Brammer, M.J., Suckling, J., Kim, J., Cleare, A.J., Walsh, N.D., Mitterschiffthaler, M.T., Andrew, C.M., Pich, E.M., Bullmore, E.T., 2007. Neural responses to happy facial expressions in major depression following antidepressant treatment. Am. J. Psychiatry 164, 599–607. https://doi.org/10.1176/ajp.2007.164.4.599

Fu, C.H.Y., Williams, S.C.R., Cleare, A.J., Brammer, M.J., Walsh, N.D., Kim, J., Andrew, C.M., Pich, E.M., Williams, P.M., Reed, L.J., Mitterschiffthaler, M.T., Suckling, J., Bullmore, E.T., 2004. Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. Arch. Gen. Psychiatry 61, 877–889. https://doi.org/10.1001/archpsyc.61.9.877

Furey, M.L., Drevets, W.C., Hoffman, E.M., Frankel, E., Speer, A.M., Zarate, C.A., 2013. Potential of pretreatment neural activity in the visual cortex during emotional processing to predict treatment response to scopolamine in major depressive disorder. JAMA Psychiatry 70, 280–290. https://doi.org/10.1001/2013.jamapsychiatry.60

Furey, M.L., Drevets, W.C., Szczepanik, J., Khanna, A., Nugent, A., Zarate, C.A., 2015. Pretreatment Differences in BOLD Response to Emotional Faces Correlate with Antidepressant Response to Scopolamine. Int. J. Neuropsychopharmacol. 18. https://doi.org/10.1093/ijnp/pyv028

Godlewska, B.R., Browning, M., Norbury, R., Cowen, P.J., Harmer, C.J., 2016. Early changes in emotional processing as a marker of clinical response to SSRI treatment in depression. Transl. Psychiatry 6, e957. https://doi.org/10.1038/tp.2016.130

Godlewska, B.R., Norbury, R., Selvaraj, S., Cowen, P.J., Harmer, C.J., 2012. Short-term SSRI treatment normalises amygdala hyperactivity in depressed patients. Psychol. Med. 42, 2609–2617. https://doi.org/10.1017/S0033291712000591

Gyurak, A., Patenaude, B., Korgaonkar, M.S., Grieve, S.M., Williams, L.M., Etkin, A., 2016. Frontoparietal Activation During Response Inhibition Predicts Remission to Antidepressants in Patients With Major Depression. Biol. Psychiatry 79, 274–281. https://doi.org/10.1016/j.biopsych.2015.02.037

Harmer, C.J., 2008. Serotonin and emotional processing: does it help explain antidepressant drug action? Neuropharmacology 55, 1023–1028. https://doi.org/10.1016/j.neuropharm.2008.06.036

Heller, A.S., Johnstone, T., Light, S.N., Peterson, M.J., Kolden, G.G., Kalin, N.H., Davidson, R.J., 2013. Relationships between changes in sustained fronto-striatal connectivity and positive affect in major depression resulting from antidepressant treatment. Am. J. Psychiatry 170, 197–206. https://doi.org/10.1176/appi.ajp.2012.12010014

Jiang, W., Yin, Z., Pang, Y., Wu, F., Kong, L., Xu, K., 2012. Brain functional changes in facial expression recognition in patients with major depressive disorder before and after antidepressant treatment: A functional magnetic resonance imaging study. Neural Regen. Res. 7, 1151–1157. https://doi.org/10.3969/j.issn.1673-5374.2012.15.005

Karim, H.T., Andreescu, C., Tudorascu, D., Smagula, S.F., Butters, M.A., Karp, J.F., Reynolds, C., Aizenstein, H.J., 2017. Intrinsic functional connectivity in late-life depression: trajectories over the course of pharmacotherapy in remitters and non-remitters. Mol. Psychiatry 22, 450–457. https://doi.org/10.1038/mp.2016.55

Keedwell, P., Drapier, D., Surguladze, S., Giampietro, V., Brammer, M., Phillips, M., 2009. Neural markers of symptomatic improvement during antidepressant therapy in severe depression: subgenual cingulate and visual cortical responses to sad, but not happy, facial stimuli are correlated with changes in symptom score. J. Psychopharmacol. Oxf. Engl. 23, 775–788. https://doi.org/10.1177/0269881108093589

Keedwell, P.A., Drapier, D., Surguladze, S., Giampietro, V., Brammer, M., Phillips, M., 2010. Subgenual cingulate and visual cortex responses to sad faces predict clinical outcome during antidepressant treatment for depression. J. Affect. Disord. 120, 120–125. https://doi.org/10.1016/j.jad.2009.04.031

Lai, C.-H., Wu, Y.-T., 2012. Frontal regional homogeneity increased and temporal regional homogeneity decreased after remission of first-episode drug-naïve major depressive disorder with panic disorder patients under duloxetine therapy for 6 weeks. J. Affect. Disord. 136, 453–458. https://doi.org/10.1016/j.jad.2011.11.004

Lemogne, C., Mayberg, H., Bergouignan, L., Volle, E., Delaveau, P., Lehéricy, S., Allilaire, J.-F., Fossati, P., 2010. Self-referential processing and the prefrontal cortex over the course of depression: a pilot study. J. Affect. Disord. 124, 196–201. https://doi.org/10.1016/j.jad.2009.11.003

Li, B., Liu, L., Friston, K.J., Shen, H., Wang, L., Zeng, L.-L., Hu, D., 2013. A treatment-resistant default mode subnetwork in major depression. Biol. Psychiatry 74, 48–54. https://doi.org/10.1016/j.biopsych.2012.11.007

Light, S.N., Heller, A.S., Johnstone, T., Kolden, G.G., Peterson, M.J., Kalin, N.H., Davidson, R.J., 2011. Reduced right ventrolateral prefrontal cortex activity while inhibiting positive affect is associated with improvement in hedonic capacity after 8 weeks of antidepressant treatment in major depressive disorder. Biol. Psychiatry 70, 962–968. https://doi.org/10.1016/j.biopsych.2011.06.031

Lisiecka, D., Meisenzahl, E., Scheuerecker, J., Schoepf, V., Whitty, P., Chaney, A., Moeller, H.-J., Wiesmann, M., Frodl, T., 2011. Neural correlates of treatment outcome in major depression. Int. J. Neuropsychopharmacol. 14, 521–534. https://doi.org/10.1017/S1461145710001513

Lopez, A.D., Mathers, C.D., Ezzati, M., Jamison, D.T., Murray, C.J.L., 2006. Measuring the Global Burden of Disease and Risk Factors, 1990–2001, in: Lopez, A.D., Mathers, C.D.,

Ezzati, M., Jamison, D.T., Murray, C.J. (Eds.), Global Burden of Disease and Risk Factors. World Bank, Washington (DC).

López-Solà, M., Pujol, J., Hernández-Ribas, R., Harrison, B.J., Contreras-Rodríguez, O., Soriano-Mas, C., Deus, J., Ortiz, H., Menchón, J.M., Vallejo, J., Cardoner, N., 2010. Effects of duloxetine treatment on brain response to painful stimulation in major depressive disorder. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 35, 2305–2317. https://doi.org/10.1038/npp.2010.108

Mayberg, H.S., 2009. Targeted electrode-based modulation of neural circuits for depression. J. Clin. Invest. 119, 717–725. https://doi.org/10.1172/JCI38454

Mayberg, H.S., 1997. Limbic-cortical dysregulation: a proposed model of depression. J. Neuropsychiatry Clin. Neurosci. 9, 471–481. https://doi.org/10.1176/jnp.9.3.471

Miller, J.M., Schneck, N., Siegle, G.J., Chen, Y., Ogden, R.T., Kikuchi, T., Oquendo, M.A., Mann, J.J., Parsey, R.V., 2013. fMRI response to negative words and SSRI treatment outcome in major depressive disorder: a preliminary study. Psychiatry Res. 214, 296–305.

Miskowiak, K.W., Macoveanu, J., Vinberg, M., Assentoft, E., Randers, L., Harmer, C.J., Ehrenreich, H., Paulson, O.B., Knudsen, G.M., Siebner, H.R., Kessing, L.V., 2016a. Effects of erythropoietin on memory-relevant neurocircuitry activity and recall in mood disorders. Acta Psychiatr. Scand. 134, 249–259. https://doi.org/10.1111/acps.12597

Miskowiak, K.W., Vinberg, M., Glerup, L., Paulson, O.B., Knudsen, G.M., Ehrenreich, H., Harmer, C.J., Kessing, L.V., Siebner, H.R., Macoveanu, J., 2016b. Neural correlates of improved executive function following erythropoietin treatment in mood disorders. Psychol. Med. 46, 1679–1691. https://doi.org/10.1017/S0033291716000209

Murray, C.J., Lopez, A.D., 1997. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet Lond. Engl. 349, 1498–1504. https://doi.org/10.1016/S0140-6736(96)07492-2

Murrough, J.W., Collins, K.A., Fields, J., DeWilde, K.E., Phillips, M.L., Mathew, S.J., Wong, E., Tang, C.Y., Charney, D.S., Iosifescu, D.V., 2015. Regulation of neural responses to emotion perception by ketamine in individuals with treatment-resistant major depressive disorder. Transl. Psychiatry 5, e509. https://doi.org/10.1038/tp.2015.10

Perkins, A.M., Arnone, D., Smallwood, J., Mobbs, D., 2015. Thinking too much: self-generated thought as the engine of neuroticism. Trends Cogn. Sci. 19, 492–498. https://doi.org/10.1016/j.tics.2015.07.003

Phillips, M.L., Drevets, W.C., Rauch, S.L., Lane, R., 2003. Neurobiology of emotion perception II: Implications for major psychiatric disorders. Biol. Psychiatry 54, 515–528.

Posner, J., Hellerstein, D.J., Gat, I., Mechling, A., Klahr, K., Wang, Z., McGrath, P.J., Stewart, J.W., Peterson, B.S., 2013. Antidepressants normalize the default mode network in patients with dysthymia. JAMA Psychiatry 70, 373–382. https://doi.org/10.1001/jamapsychiatry.2013.455

Qin, J., Shen, H., Zeng, L.-L., Jiang, W., Liu, L., Hu, D., 2015. Predicting clinical responses in major depression using intrinsic functional connectivity. Neuroreport 26, 675–680. https://doi.org/10.1097/WNR.0000000000000407

Ramasubbu, R., Burgess, A., Gaxiola-Valdez, I., Cortese, F., Clark, D., Kemp, A., Goodyear, B., Macqueen, G., Bech-Hansen, N.T., Foster, J., Diwadkar, V.A., 2016. Amygdala responses to quetiapine XR and citalopram treatment in major depression: the role

of 5-HTTLPR-S/Lg polymorphisms. Hum. Psychopharmacol. 31, 144–155. https://doi.org/10.1002/hup.2521

Rizvi, S.J., Salomons, T.V., Konarski, J.Z., Downar, J., Giacobbe, P., McIntyre, R.S., Kennedy, S.H., 2013. Neural response to emotional stimuli associated with successful antidepressant treatment and behavioral activation. J. Affect. Disord. 151, 573–581. https://doi.org/10.1016/j.jad.2013.06.050

Robertson, B., Wang, L., Diaz, M.T., Aiello, M., Gersing, K., Beyer, J., Mukundan, S., McCarthy, G., Doraiswamy, P.M., 2007. Effect of bupropion extended release on negative emotion processing in major depressive disorder: a pilot functional magnetic resonance imaging study. J. Clin. Psychiatry 68, 261–267.

Roiser, J.P., Elliott, R., Sahakian, B.J., 2012. Cognitive mechanisms of treatment in depression. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 37, 117–136. https://doi.org/10.1038/npp.2011.183

Rosenblau, G., Sterzer, P., Stoy, M., Park, S., Friedel, E., Heinz, A., Pilhatsch, M., Bauer, M., Ströhle, A., 2012. Functional neuroanatomy of emotion processing in major depressive disorder is altered after successful antidepressant therapy. J. Psychopharmacol. Oxf. Engl. 26, 1424–1433. https://doi.org/10.1177/0269881112450779

Ruhé, H.G., Booij, J., Veltman, D.J., Michel, M.C., Schene, A.H., 2012. Successful pharmacologic treatment of major depressive disorder attenuates amygdala activation to negative facial expressions: a functional magnetic resonance imaging study. J. Clin. Psychiatry 73, 451–459. https://doi.org/10.4088/JCP.10m06584

Ruhé, H.G., Koster, M., Booij, J., van Herk, M., Veltman, D.J., Schene, A.H., 2014. Occupancy of serotonin transporters in the amygdala by paroxetine in association with attenuation of left amygdala activation by negative faces in major depressive disorder. Psychiatry Res. 221, 155–161. https://doi.org/10.1016/j.pscychresns.2013.12.003

Samson, A.C., Meisenzahl, E., Scheuerecker, J., Rose, E., Schoepf, V., Wiesmann, M., Frodl, T., 2011. Brain activation predicts treatment improvement in patients with major depressive disorder. J. Psychiatr. Res. 45, 1214–1222. https://doi.org/10.1016/j.jpsychires.2011.03.009

Sankar, A., Adams, T.M., Costafreda, S.G., Marangell, L.B., Fu, C.H., 2017. Effects of antidepressant therapy on neural components of verbal working memory in depression. J. Psychopharmacol. Oxf. Engl. 31, 1176–1183. https://doi.org/10.1177/0269881117724594

Schaefer, H.S., Putnam, K.M., Benca, R.M., Davidson, R.J., 2006. Event-related functional magnetic resonance imaging measures of neural activity to positive social stimuli in pre- and post-treatment depression. Biol. Psychiatry 60, 974–986. https://doi.org/10.1016/j.biopsych.2006.03.024

Sheline, Y.I., Barch, D.M., Donnelly, J.M., Ollinger, J.M., Snyder, A.Z., Mintun, M.A., 2001. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. Biol. Psychiatry 50, 651–658.

Smith, J., Browning, M., Conen, S., Smallman, R., Buchbjerg, J., Larsen, K.G., Olsen, C.K., Christensen, S.R., Dawson, G.R., Deakin, J.F., Hawkins, P., Morris, R., Goodwin, G., Harmer, C.J., 2017. Vortioxetine reduces BOLD signal during performance of the N-back working memory task: a randomised neuroimaging trial in remitted depressed patients and healthy controls. Mol. Psychiatry. https://doi.org/10.1038/mp.2017.104

Stoy, M., Schlagenhauf, F., Sterzer, P., Bermpohl, F., Hägele, C., Suchotzki, K., Schmack, K., Wrase, J., Ricken, R., Knutson, B., Adli, M., Bauer, M., Heinz, A., Ströhle, A., 2012. Hyporeactivity of ventral striatum towards incentive stimuli in unmedicated depressed patients normalizes after treatment with escitalopram. J. Psychopharmacol. Oxf. Engl. 26, 677–688. https://doi.org/10.1177/0269881111416686

Tao, R., Calley, C.S., Hart, J., Mayes, T.L., Nakonezny, P.A., Lu, H., Kennard, B.D., Tamminga, C.A., Emslie, G.J., 2012. Brain activity in adolescent major depressive disorder before and after fluoxetine treatment. Am. J. Psychiatry 169, 381–388. https://doi.org/10.1176/appi.ajp.2011.11040615

Vanderwolf, C.H., 1998. Brain, behavior, and mind: what do we know and what can we know? Neurosci. Biobehav. Rev. 22, 125–142.

Victor, T.A., Furey, M.L., Fromm, S.J., Öhman, A., Drevets, W.C., 2013. Changes in the neural correlates of implicit emotional face processing during antidepressant treatment in major depressive disorder. Int. J. Neuropsychopharmacol. 16, 2195–2208. https://doi.org/10.1017/S146114571300062X

Victor, T.A., Furey, M.L., Fromm, S.J., Ohman, A., Drevets, W.C., 2010. Relationship between amygdala responses to masked faces and mood state and treatment in major depressive disorder. Arch. Gen. Psychiatry 67, 1128–1138. https://doi.org/10.1001/archgenpsychiatry.2010.144

Wagner, G., Koch, K., Schachtzabel, C., Sobanski, T., Reichenbach, J.R., Sauer, H., Schlösser, R.G.M., 2010. Differential effects of serotonergic and noradrenergic antidepressants on brain activity during a cognitive control task and neurofunctional prediction of treatment outcome in patients with depression. J. Psychiatry Neurosci. JPN 35, 247–257.

Walsh, N.D., Williams, S.C.R., Brammer, M.J., Bullmore, E.T., Kim, J., Suckling, J., Mitterschiffthaler, M.T., Cleare, A.J., Pich, E.M., Mehta, M.A., Fu, C.H.Y., 2007. A longitudinal functional magnetic resonance imaging study of verbal working memory in depression after antidepressant therapy. Biol. Psychiatry 62, 1236–1243. https://doi.org/10.1016/j.biopsych.2006.12.022

Wang, L., Li, K., Zhang, Q., Zeng, Y., Dai, W., Su, Y., Wang, G., Tan, Y., Jin, Z., Yu, X., Si, T., 2014a. Short-term effects of escitalopram on regional brain function in first-episode drug-naive patients with major depressive disorder assessed by resting-state functional magnetic resonance imaging. Psychol. Med. 44, 1417–1426. https://doi.org/10.1017/S0033291713002031

Wang, L., Li, K., Zhang, Q., Zeng, Y., Dai, W., Su, Y., Wang, G., Tan, Y., Jin, Z., Yu, X., Si, T., 2014b. Short-term effects of escitalopram on regional brain function in first-episode drug-naive patients with major depressive disorder assessed by resting-state functional magnetic resonance imaging. Psychol. Med. 44, 1417–1426. https://doi.org/10.1017/S0033291713002031

Wang, L., Li, X., Li, K., Su, Y., Zeng, Y., Zhang, Q., Wang, G., Jin, Z., Kong, Q., Si, T., 2017. Mapping the effect of escitalopram treatment on amplitude of low-frequency fluctuations in patients with depression: a resting-state fMRI study. Metab. Brain Dis. 32, 147–154. https://doi.org/10.1007/s11011-016-9871-5

Wang, L., Xia, M., Li, K., Zeng, Y., Su, Y., Dai, W., Zhang, Q., Jin, Z., Mitchell, P.B., Yu, X., He, Y., Si, T., 2015. The effects of antidepressant treatment on resting-state functional

brain networks in patients with major depressive disorder. Hum. Brain Mapp. 36, 768–778. https://doi.org/10.1002/hbm.22663

Wang, Y., Xu, C., Cao, X., Gao, Q., Li, J., Liu, Z., Sun, N., Ren, Y., Zhang, K., 2012. Effects of an antidepressant on neural correlates of emotional processing in patients with major depression. Neurosci. Lett. 527, 55–59. https://doi.org/10.1016/j.neulet.2012.08.034

Warden, D., Rush, A.J., Trivedi, M.H., Fava, M., Wisniewski, S.R., 2007. The STAR*D Project results: a comprehensive review of findings. Curr. Psychiatry Rep. 9, 449–459.

Williams, L.M., Korgaonkar, M.S., Song, Y.C., Paton, R., Eagles, S., Goldstein-Piekarski, A., Grieve, S.M., Harris, A.W.F., Usherwood, T., Etkin, A., 2015. Amygdala Reactivity to Emotional Faces in the Prediction of General and Medication-Specific Responses to Antidepressant Treatment in the Randomized iSPOT-D Trial. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 40, 2398–2408. https://doi.org/10.1038/npp.2015.89

Wise, T., Cleare, A.J., Herane, A., Young, A.H., Arnone, D., 2014. Diagnostic and therapeutic utility of neuroimaging in depression: an overview. Neuropsychiatr. Dis. Treat. 10, 1509–1522. https://doi.org/10.2147/NDT.S50156

Wise, T., Marwood, L., Perkins, A.M., Herane-Vives, A., Joules, R., Lythgoe, D.J., Luh, W.-M., Williams, S.C.R., Young, A.H., Cleare, A.J., Arnone, D., 2017a. Instability of default mode network connectivity in major depression: a two-sample confirmation study. Transl. Psychiatry 7, e1105. https://doi.org/10.1038/tp.2017.40

Wise, T., Radua, J., Via, E., Cardoner, N., Abe, O., Adams, T.M., Amico, F., Cheng, Y., Cole, J.H., de Azevedo Marques Périco, C., Dickstein, D.P., Farrow, T.F.D., Frodl, T., Wagner, G., Gotlib, I.H., Gruber, O., Ham, B.J., Job, D.E., Kempton, M.J., Kim, M.J., Koolschijn, P.C.M.P., Malhi, G.S., Mataix-Cols, D., McIntosh, A.M., Nugent, A.C., O'Brien, J.T., Pezzoli, S., Phillips, M.L., Sachdev, P.S., Salvadore, G., Selvaraj, S., Stanfield, A.C., Thomas, A.J., van Tol, M.J., van der Wee, N.J.A., Veltman, D.J., Young, A.H., Fu, C.H., Cleare, A.J., Arnone, D., 2017b. Common and distinct patterns of grey-matter volume alteration in major depression and bipolar disorder: evidence from voxel-based meta-analysis. Mol. Psychiatry 22, 1455–1463. https://doi.org/10.1038/mp.2016.72

Wise, T., Taylor, M.J., Herane-Vives, A., Gammazza, A.M., Cappello, F., Lythgoe, D.J., Williams, S.C., Young, A.H., Cleare, A.J., Arnone, D., 2018. Glutamatergic hypofunction in medication-free major depression: Secondary effects of affective diagnosis and relationship to peripheral glutaminase. J. Affect. Disord. 234, 214–219. https://doi.org/10.1016/j.jad.2018.02.059

Yang, R., Zhang, H., Wu, X., Yang, J., Ma, M., Gao, Y., Liu, H., Li, S., 2014. Hypothalamus-anchored resting brain network changes before and after sertraline treatment in major depression. BioMed Res. Int. 2014, 915026. https://doi.org/10.1155/2014/915026

Table 1: *Functional MRI of pharmacological treatment in major depression with emotion processing tasks*

Study	Diagnosis	Comorbidities	fMRI Task	Scanner (T)	N. Cases/controls Mean age	Analyses	Results in major depression
Sheline et al., 2001	DSM IV	Excluded	Emotional Faces	1.5T	11/11 40 years	Amygdale (ROI)	↓ amygdale activation after 8-week treatment with Sertraline.
Davidson et al., 2003	DSM IV	Dysthymia Specific phobias	Emotional Pictures	1.5T	12/5 38 years	WB	↓ activation in the left Ins and left ACC in response to negative pictures at baseline in which normalised after 8-week treatment with Venlafaxine.
Fu et al., 2004	DSM IV	Excluded	Sad Faces	1.5T	19/19 43 years	WB	↓ activation in amygdala, ventral striatum, Ins, caudate nucleus, thalamus, cingulate cortex, precentral and post central gyri, inferior parietal lobule, which normalised after a course of 8-week treatment with Fluoxetine.
Schaefer et al., 2006	DSM IV	GAD, BED	Emotional pictures (social content)	1.5T	9/14 36 years	WB	↓ in prefrontal temporal, and parietal cortices, insula, basal ganglia, and hippocampus following treatment with Venlafaxine for 22 weeks.
Anand et al., 2007	DSM IV	Excluded	Negative pictures	1.5T	12/11 30 years	Amygdale, pACC, mTHA, PS, (ROI)	↓ activation in left amygdala, pACC and PS after 6-week treatment with Sertraline.
Fu et al., 2007	DSM IV	Excluded	Happy faces	1.5T	19/19 43 years	WB	↓ activation in lingual gyrus, cuneus, precuneus and PCC after following 8-week treatment with Fluoxetine
Fales et al., 2009	DSM IV	Excluded	Emotion interference task	3T	23/18 36 years	Amygdale, ACC, DLPFC, amygdala (ROI)	↑ activation in the dorsolateral prefrontal cortex and left amygdala which normalised following 8-week treatment with Escitalopram, Sertraline, and Paroxetine.
Victor et al., 2010	DSM IV	Anxiety disorders	Emotional faces	3T	22 /25 31years	Amygdale (ROI)	↓ activation in amygdale with sad faced and ↑ with happy faces after 8-week treatment with Sertraline.
Arnone et al., 2012	DSM IV	Excluded	Emotional faces	1.5T	38 /54 36 years	WB, amygdale (ROI)	Normalisation of ↑ neural activity in bilateral amygdala to sad faces following 8-week treatment with Citalopram.
Rosenblau et al., 2012	DSM IV	Excluded	Emotional pictures	1.5T	12/12 43.5 years	mFC, OFC, DLPFC, ACC, amygdale (ROI)	↓ activation to negative pictures in DLPFC, right OFC after 8-week treatment with Escitalopram.
Ruhe et al., 2012	DSM IV	Anxiety disorders AD, CD	Emotional faces (implicit)	3T	22/22 43 years	Amygdale (ROI)	↓ activation in left amygdala associated with response to treatment after 12 weeks treatment with Paroxetine.
Wang et al., 2012	DSM IV	Excluded	Emotional judgement	3T	18/18 32 years	WB	↑ activation in the right middle frontal gyrus, right inferior temporal gyrus, right

							precuneus and inferior parietal lobule after treatment in response to negative stimuli and ↓ activation in response to positive pictures in the right Ins, left caudate head and left ACC after 8 weeks treatment with Fluoxetine.
Heller et al., 2013	DSM IV	Excluded	Emotion regulation	3T	21/14 31 years	NA (ROI)	↑ activation in the NA after 8 weeks of treatment with Fluoxetine or Venlafaxine and ↑ fronto-striatal connectivity.
Victor et al., 2013	DSM IV	Anxiety disorders PTSD	Emotional faces	3T	10/10 33 years	WB, pACC (ROI)	The right lateral frontal polar cortex showed ↑ neural activity following treatment with Sertraline for 8 weeks.
Fu et al., 2015	DSM IV	Excluded	Emotional Stroop	3T	32/25 40 years	WB	↑ activation in the PCC, parahippocampal cortex, and precuneus after treatment with Duloxetine.
Williams et al., 2015	DSM IV	Excluded	Emotional faces 3T	3T	80/34 33 years	Amygdala (ROI)	↓ activation in the amygdala in responders to happiness, fear and anger after 8 weeks treatment with Escitalopram, Sertraline, or Venlafaxine.
Delaveau et al., 2016	DSM IV	Anxiety disorders	Emotional pictures	3T	25/14 41 years	DMPFC, VMPFC, PCC, ACC, VLPFC, DLPFC (ROI)	Agomelatine showed a significant tendency to decrease ↓ activation in VLPFC after 1 week of Agomelatine, and ↑ activation in ACC and ↓ in DLPFC after 7 weeks.
Godlewska et al., 2016	DSM IV	Anxiety disorders	Emotional faces	3T	35/29 30 years	WB, amygdale, ACC, Ins (ROI)	Depressed subjects were treated with escitalopram and showed a ↓ activation to fearful vs. happy faces following 7-day Escitalopram treatment in the left amygdala, Ins, ACC, PCC insula, bilateral supra-marginal gyri and bilateral thalamus.

GAD: generalised anxiety disorder; BED: binge eating disorder; AD: alcohol dependence, CD: cannabis dependence; PTSD: post-traumatic stress disorder; WB: whole brain; ROI: region of interest; pACC: pregenual anterior cingulate cortex; ACC: anterior cingulate cortex; mTHA: medial thalamus; PS: pallido striatum; DLPFC: dorsolateral prefrontal cortex; DMPFC: dorsomedial prefrontal cortex; PCC: posterior cingulate cortex, mFC: medial frontal cortex; VMPFC: ventromedial prefrontal cortex; VLPFC: ventrolateral prefrontal cortex; OFC: orbitofrontal cortex; NA: nucleus accumbens; Ins: insule

Table 2: *Functional MRI of pharmacological treatment in major depression with non-emotional tasks*

Study	Diagnosis	Comorbidities	fMRI Task	Scanner (T)	N. Cases/controls Mean age	Analyses	Results in major depression
Walsh et al., 2007	DSM IV	Excluded	N-Back verbal working memory	1.5T	20/20 44 years	WB	↑ in activation in left caudate and right thalamus after 8 weeks of Fluoxetine treatment.
Lemogne et al., 2010	DSM IV	Not excluded	Self-judgement task	1.5T	8/8 33 years	ROI in prefrontal cortex	↓ activation in left DLPFC and ↑ in dorsomedial frontal gyrus with the self vs. general condition after 9 weeks of treatment with SSRIs, SNRIs and tricyclics.
Lopez-Sola et al., 2010	DSM IV	Excluded	Pain condition	1.5T	13/20 45	WB	↓ activation in a range of cortical regions including ventromedial prefrontal cortex, subgenual and pACC, middle temporal gyrus, DLPFC, frontal and temporal opercula, Ins, left hippocampus, ventral basal ganglia, hypothalamus at week 1 and similarly at week 8 following treatment with Duloxetine.
Wagner et al., 2010	DSM IV	Excluded	Stroop colour-words	1.5T	20/20 39	WB	↓ amygdala-hippocampus following 6-week treatment with Citalopram.
Stoy et al., 2012	DSM IV	Excluded	Monetary task	1.5T	15/15 42	ROI in ventral striatum	↓ activation in ventral striatum following anticipation of loss which normalised after treatment with Escitalopram for 6 weeks.
Gyurak et al., 2016	DSM IV	Not excluded	Go/NoGo task, Oddball task Selective working memory Task	3T	80/34 32.5	WB	↓ activation in the DLPFC in non-remitters which persisted after 8-week treatment with Escitalopram, Sertraline, or Venlafaxine extended release with the inhibitory NoGo task.
Sankar et al., 2017	DSM IV	Excluded	Sternberg task	3T	23/22 40	WB	↓ activation in healthy participants over 12 weeks and no changes in affected individuals treated with Duloxetine in the left middle frontal gyrus, the right middle cingulum, left inferior temporal gyrus, right superior temporal pole, caudate, right thalamus, and cerebellum.

WB: whole brain; ROI: region of interest; pACC: pregenual anterior cingulate cortex; ACC: anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex; Ins: insule

Table 3: *Resting state analysis*

Study	Diagnosis	Comorbidities	Connectivity	Scanner (T)	N. Cases/controls Mean age	Analyses	Results in major depression
Anand et al., 2005	DSM IV	Excluded	Seed analysis	1.5T	12/11 30 years	Amygdale, pACC, mTHA, PS, (ROI)	↑ connectivity between ACC and left and right mTHA following treatment with Sertraline for 6 weeks.
Lai and Wu, 2012	DSM IV	Panic disorder	Regional homogeneity	3T	15/15 36	WB	↑ regional homogeneity in right superior frontal cortex, right mFC and ↓ in the right superior temporal cortex after 6 weeks treatment with Duloxetine.
Li et al., 2013	DSM IV	Excluded	Independent component analysis	1.5T	24/29 32	Default mode network	↑ connectivity in a posterior network comprising the bilateral precuneus and in an anterior network which included the medial prefrontal cortex. Following 12-week treatment with Paroxetine, Citalopram, Venlafaxine or Duloxetine only connectivity in the posterior network normalised in 16 patients scanned twice.
Fu et al., 2015	DSM IV	Excluded	Independent component analysis	3T	32/25 40	Default mode network Eyes closed	↓ connectivity in the default mode network between right DLPFC, right superior frontal premotor cortex and left inferior frontal gyrus after 12 weeks of treatment with Duloxetine.
Wang et al., 2015	DSM IV	Excluded	Graph theory functional connectivity strength	3T	20/20 35	Seed-based connectivity analyses	↓ functional connectivity strength in the bilateral DMPFC following treatment with Escitalopram after 8 weeks. The bilateral hippocampus followed an inverse pattern.
Cheng et al., 2017	DSM IV	Excluded	Fractional amplitude of low-frequency fluctuation	1.5T	74/74 29	WB	↓ signal following acute (5H) and sub-chronic (4W and 8W) Escitalopram treatment administration in the bilateral post-central gyrus and left superior temporal gyrus and ↑ in a vast area of the prefrontal cortex incorporating DMPFC and DLPFC.

WB: whole brain; ROI: region of interest; ACC: anterior cingulate cortex; mTHA: medial thalamus; DLPFC: dorsolateral prefrontal cortex; DMPFC: dorsomedial prefrontal cortex; PCC: posterior cingulate cortex, mFC: medial frontal cortex;

Highlights

- This work summarises the literature of longitudinal functional magnetic resonance imaging studies in major depression to identify brain regions where aberrant neural activity normalises after clinical response following treatment with pharmacological compounds with known antidepressant properties.
- Hyperactivity in regions such as the amygdala and the ventral components of the anterior cingulate cortex were some of the most replicated findings of functional MRI studies in major depression and normalisation of aberrant activity one of the best predictive biomarkers of treatment response.